The Rejection Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1 and 3-10 under 35 U.S.C. §103(a) as allegedly being obvious over Zhu et al., August 12, 1999, *Nature* 400:687-693 ("Zhu") in view of Hustad et al., U.S. Patent Number 6,087,122, filed July 21, 1999 ("Hustad"). The Examiner states that Zhu teaches a human Smad ubiquitin ligase, hSmurf1, that is a HECT E3 kinase. Further, Zhu teaches that hSmurf1 interacts with Smads 1 and 5 through interactions between the Smad PY motif and the WW domains of the ligase. The Examiner contends that Hustad teaches human E3 ubiquitin protein ligase biomolecules can be used in screening assays to identify "blockers, antagonists, or inhibitors which bind, emulate substrate, or otherwise inactivate or compete with the biomolecule" (column 14, ll. 52-60). The Examiner also contends that Hustad teaches the use of E3 ubiquitin protein ligase, immunogenic fragments, or oligopeptides for screening therapeutic compounds in assays in which the fragment is free or bound and the formation of binding complexes are tested and teaches the use of ELISAs and radiolabelling.

Applicants submit that Zhu and Hustad are not applicable prior art references. Zhu was published on August 12, 1999, which is within one year of the effective filing date of August 30, 1999 of the present application. Hustad was filed on July 12, 1999, which is also within one year of the effective filing date of the present application. The claimed invention of the present application was conceived and reduced to practice in the United States prior to July 21, 1999, which is the earlier of the two relative reference dates. Applicants respectfully submit that the cited art are not references that may be used as prior art for the present application. Therefore, the Examiner's rejection is obviated and should be withdrawn.

The Rejections Under 35 U.S.C. §112, First Paragraph

Claims 1-10 are rejected under 35 U.S.C. §112, first paragraph, as not being enabled by the specification. The Examiner contends that the specification does not reasonably provide enablement for methods using variants of either a HECT E3 ubiquitin ligase domain or of a polypeptide comprising such a domain. Specifically, the Examiner contends that Applicants have described several WW domains, but have not described the structural characteristics or conserved regions of these sequences so that one of skill in the art would be

able to predict which variants would function as claimed. Thus it would require undue experimentation for one of skill in the art to practice the invention commensurate with the scope of the claims. Applicants respectfully submit that the Examiner's rejection is traversed and should be withdrawn.

The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *See U.S. v. Telectronics Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988).

Applicants submit that the specification clearly describes the structural characteristics of the variants of the HECT E3 domain so that one of skill in the art would be able to practice the invention of claims 1-10. The specification at page 13, second full paragraph through page 16, first paragraph describe the domains.

> "Within the assays provided herein, a polypeptide comprising a WW domain may be a full length HECT E3 ubiquitin ligase, a portion thereof that comprises a WW domain, or a variant of such a polypeptide in which the WW domain is modified by one or more substitutions, additions, insertions and/or deletions such that the ability of the variant to bind to a Smad PY motif is not substantially diminished (i.e., is enhanced, unchanged or diminished by no more than 10%), relative to the native WW domain sequence."

See page 14, end of the first incomplete paragraph. The specification continues to describe variants of the WW domain.

> "... A WW domain ... polypeptide variant contains conservative substitutions. A 'conservative substitution' is one in which an amino acid is substituted for another amino acid that has similar properties, such that on skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. "

See page 15, second paragraph (emphasis added). The specification continues with a description of how the changes can occur. *See* page 15, the remaining portion of the second paragraph. As pointed out by the Examiner, Applicants have described several WW domains. *See* Office action of December 1, 2000, point 7, l. 6. However, the Examiner reference to structural characteristics or conserved regions is inappropriate. *See* Office action of December 1, 2000, point 7, ll. 6-8. As emphasize above, Applicants describe conservative changes of amino acids in these sequences not changes in conservative regions.

Applicants submit that the variants of the WW domain in claim 1 *are adequately described* and it would not be undue experimentation for any person skilled in the art to use the claimed method. Therefore, Applicants respectfully submit the Examiner's rejection of claim 1 under 35 U.S.C. §112, first paragraph should be withdrawn. Applicants further submit that the Examiner's rejection of claims 2, 3, 5-7, 9, and 10, dependent upon claim 1, claim 4, dependent upon claim 3, and claim 8, dependent upon claim 6 or 7, should also be withdrawn.

The Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 1-10 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Use of the terms "HECT E3 ubiquitin ligase WW domain or variant thereof" and "SMAD PY motif" is allegedly indefinite because they only describe the protein of interest by an arbitrary name. Applicants have amended claim 1 so that the above terms are associated with specific sequence identification numbers. Specifically, "HECT E3 ubiquitin ligase WW domain or variant thereof" refers to SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 and "SMAD PY motif" refers to SEQ ID NO:14, 15, 16, 17, 20, 21, 22, 23, 24, or 25. Applicants respectfully submit that the reference to "HECT E3 ubiquitin ligase WW domain or variant thereof" and "SMAD PY motif" in claim 1 are no longer indefinite and the Examiner's rejection should be removed. Applicants further submit that the Examiner's rejection of claims 2, 3, 5-7, 9, and 10, dependent upon claim 1, claim 4, dependent upon claim 3, and claim 8, dependent upon claim 6 or 7, should also be withdrawn.

CONCLUSION

Applicants believe that each ground for objection or rejection has been overcome. If any outstanding issues remain, the Examiner is invited to telephone the undersigned at the telephone number indicated below to discuss the same.

Respectfully submitted,

Date June 1, 2001

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Enclosures

APPENDIX A: MARKED-UP AMENDED CLAIMS AS OF MAY 1, 2001

(U.S. APPLICATION NO. 09/385,918; ATTORNEY DOCKET NO. 10624-048)

1. (Amended) A method for screening for an agent that modulates [TGF-β- and/or] BMP-mediated signaling, comprising the steps of:

(a) contacting

(i) a first polypeptide comprising a HECT E3 ubiquitin ligase WW domain; SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13, or a variant thereof in which the ability of the polypeptide to bind to a Smad protein is not substantially diminished relative to the HECT E3 ubiquitin ligase;

(ii) a second polypeptide comprising a Smad PY motif; SEQ ID NO:14, 15, 16, 17, 20, 21, 22, 23, 24, or 25, or a variant thereof in which the ability of the polypeptide to bind to an E3 ubiqitin ligase is not substantially diminished relative to a native Smad protein comprising the PY motif; and

(iii) a candidate agent; under conditions that permit a detectable level of binding of the first polypeptide to the second polypeptide in the absence of candidate agent;

(b) determining a level of binding of the first polypeptide to the second polypeptide; and

(c) comparing the level of binding to a control level of binding of the first polypeptide to the second polypeptide in the absence of candidate agent, and therefrom determining whether the candidate agent modulates [TGF-β- and/or] BMP-mediated signaling.

APPENDIX B: PENDING CLAIMS AS OF MAY 1, 2001

(U.S. APPLICATION NO. 09/385,918; ATTORNEY DOCKET NO. 10624-048)

1. A method for screening for an agent that modulates BMP-mediated signaling, comprising the steps of:

(a) contacting

(i) a first polypeptide comprising a HECT E3 ubiquitin ligase WW domain; SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13, or a variant thereof in which the ability of the polypeptide to bind to a Smad protein is not substantially diminished relative to the HECT E3 ubiquitin ligase;

(ii) a second polypeptide comprising a Smad PY motif; SEQ ID NO:14, 15, 16, 17, 20, 21, 22, 23, 24, or 25, or a variant thereof in which the ability of the polypeptide to bind to an E3 ubiqitin ligase is not substantially diminished relative to a native Smad protein comprising the PY motif; and

(iii) a candidate agent; under conditions that permit a detectable level of binding of the first polypeptide to the second polypeptide in the absence of candidate agent;

(b) determining a level of binding of the first polypeptide to the second polypeptide; and

(c) comparing the level of binding to a control level of binding of the first polypeptide to the second polypeptide in the absence of candidate agent, and therefrom determining whether the candidate agent modulates BMP-mediated signaling.

2. A method according to claim 1, wherein the HECT E3 ubiquitin ligase WW domain comprises the sequence

GPLPXGWEX$_3$tttGtXYYhXHNTtTTtWXtPt (SEQ ID NO:2)

wherein each t is an independently selected polar amino acid residue (e.g., S, H, PO, D, E, T or Y), h is a hydrophobic residue (e.g., I, V, L or M) and each X is an independently selected amino acid residue.

3. A method according to claim 1, wherein the Smad PY motif comprises the sequence Ser/Thr-Pro-Pro-Pro-Pro/Ala/Gly-Tyr (SEQ ID NO:15), wherein Ser/Thr is an

amino acid residue that is serine or threonine and Pro/Ala/Gly is an amino acid residue that is selected from the group consisting of proline, alanine and glycine.

4. A method according to claim 3, wherein the Smad PY motif comprises the sequence TPPPAY (SEQ ID NO:16) or TPPPGY (SEQ ID NO:18).

5. A method according to claim 1, wherein the candidate agent is a small molecule within a combinatorial library.

6. A method according to claim 1, wherein the first polypeptide is immobilized on a solid support and the second polypeptide comprises a tag.

7. A method according to claim 1, wherein the second polypeptide is immobilized on a solid support and the first polypeptide comprises a tag.

8. A method according to claim 6 or claim 7, wherein the tag is biotin or a radioactive group.

9. A method according to claim 1, wherein the level of binding is determined via a two-antibody sandwich assay.

10. A method according to claim 1, wherein the level of binding is determined via a competitive assay.